LETTER TO THE EDITOR

Varicella-zoster and herpes simplex virus reactivation post-COVID-19 vaccination: a review of 40 cases in an International Dermatology Registry

Editor,

Since December 2020, the American Academy of Dermatology and the International League of Dermatologic Societies' COVID-19 Dermatology Registry has tracked dermatologic reactions post-COVID-19 vaccination. Within months, a variety of cutaneous manifestations were reported after the Moderna and Pfizer-BioNTech COVID-19 vaccines.[1] As of April 2021, a total of 672 possible vaccine-related skin reactions have been reported by healthcare providers. Here, we evaluate the first 40 cases of varicella-zoster virus (VZV) and herpes simplex virus (HSV) reported in the registry after COVID-19 vaccination with either the Moderna or the Pfizer-BioNTech vaccines.

Of 40 cases of herpesvirus activation diagnosed by healthcare providers after vaccination, 35 cases were VZV reactivation and 5 cases were HSV reactivation (Table 1). The median age of patients was 46 (IQR 36–67). The majority were female (70%), white (80%), and from the United States (95%).

Among the 35 patients with VZV reactivation (Fig. 1), 19 received Pfizer-BioNTech and 16 received Moderna. Most (77%) cases occurred after the first vaccine dose only, and none of the patients had repeat viral flares after both doses. Median onset was 7 days (IQR 2–13) from vaccination to the first VZV symptom, and symptoms lasted median of 7 days (IQR 5–12). Patients were primarily treated with valacyclovir/acyclovir (86%). One patient was not planning on receiving their second vaccine dose due to VZV after the first dose. Data on prior VZV vaccination were available for 14 individuals, and of these, only one had received a VZV vaccine (live-attenuated), 7 years prior.

Of 5 patients reported with HSV reactivation post-COVID vaccine, 4 received Pfizer-BioNTech and 1 received Moderna. Four of these cases occurred after the first dose, and one case occurred only after the second dose. Median onset of first HSV symptom was 13 days (IQR 8–15) post-vaccination and lasted median of 7 days (IQR 3–7). Four patients (80%) received valacyclovir/acyclovir as treatment, and none delayed their second vaccine dose.

Table 1 Characteristics of 40 HSV and VZV Reactivation Events Reported after Moderna or Pfizer-BioNTech COVID-19 vaccination

	VZV reactivation Unique reports *N* (%) (*n* = 35)	**HSV reactivation Unique reports *N* (%) (*n* = 5)**	**Total Unique reports *N* (%) (*n* = 40)**
COVID-19 vaccine type			
Moderna	16 (46)	1 (20)	17 (42)
Pfizer	19 (54)	4 (80)	23 (58)
Reporter title			
Dermatologist	25 (71)	5 (100)	30 (75)
Other physician	9 (26)	0 (0)	9 (23)
Nurse practitioner	1 (2.9)	0 (0)	1 (2.5)
Patient age (Median, IQR)	46 (35–68)	39 (36–53)	46 (36–67)
Patient sex (Female)	24 (69)	4 (80)	28 (70)
Patient race/ethnicity			
White	28 (80)	4 (80)	32 (80)
Asian	2 (5.7)	0	2 (5.0)
Black/African American	2 (5.7)	0	2 (5.0)
Hispanic/Latino	2 (5.7)	1 (20)	3 (7.5)
Unknown	1 (2.9)	0 (0)	1 (2.5)
Patient Country			
United States	34 (97)	4 (80)	38 (95)
Canada	0	1 (20)	1 (2.5)
Saudi Arabia	1 (2.7)	0	1 (2.5)

Table 1 *Continued*

	VZV reactivation Unique reports *N* (%) (*n* = 35)	HSV reactivation Unique reports *N* (%) (*n* = 5)	Total Unique reports *N* (%) (*n* = 40)
Prior SARS-CoV-2 infection			
No	34 (97)	5 (100)	39 (98)
SARS-CoV-2 PCR+	1 (2.7)	0 (0)	1 (2.5)
Vaccine dose number associated with reaction			
First	27 (77)	4 (80)	31 (78)
Second	8 (23)	1 (20)	9 (23)
Both	0 (0)	0 (0)	0 (0)
Rash location†			
Face	3 (8.6)	4 (80)	7 (18)
Head	4 (11)	0 (0)	4 (10)
Neck	2 (5.7)	0 (0)	2 (5.0)
Vaccinated arm	3 (8.6)	0 (0)	3 (7.5)
Non-vaccinated arm	1 (2.9)	0 (0)	1 (2.5)
Chest	14 (40)	0 (0)	14 (35)
Abdomen	10 (29)	0 (0)	10 (25)
Back	16 46)	0 (0)	16 (40)
Buttocks	3 (8.6)	0 (0)	3 (7.5)
Leg	3 (8.6)	0 (0)	3 (7.5)
Oral mucosa	0 (0)	1 (20)	1 (2.5)
Vaccine allergy history			
None	35 (100)	5 (100)	40 (100)
Past medical history			
None	14 (40)	4 (80)	18 (45)
Hypertension	7 (20)	1 (20)	8 (20)
Rheumatologic disease	3 (8.6)	0 (0)	3 (7.5)
Morbid obesity	2 (5.7)	0 (0)	2 (5.0)
Diabetes mellitus	2 (5.7)	0 (0)	2 (5.0)
Cardiovascular disease	1 (2.9)	0 (0)	1 (2.5)
Obstructive lung disease	1 (2.9)	0 (0)	1 (2.5)
Chronic renal insufficiency	1 (2.9)		1 (2.5)
Liver disease	1 (2.9)	0 (0)	1 (2.5)
Immunodeficiency	1 (2.9)	0 (0)	1 (2.5)
Other	8 (23)	0 (0)	8 (20)
Treatment			
Valacyclovir/Acyclovir	30 (86)	4 (80)	34 (85)
Topical steroids	1 (2.9)	0 (0)	1 (2.5)
Acetaminophen	2 (5.7)	0 (0)	2 (5.0)
Gabapentin	4 (11)	0 (0)	4 (10)
None	3 (8.6)	1 (20)	4 (10)

†Providers were able to check off multiple rash locations for each patient.

One limitation is that the registry did not routinely ascertain whether VZV/HSV was diagnosed by the reporter based on laboratory testing (e.g. PCR) or on clinical grounds alone, although clinical diagnosis of zoster without laboratory testing has a reported positive predictive value of 86%–92%.[2,3] Additional limitations are incomplete VZV vaccination history and immune status data, which hinder the ability to draw conclusions about the relationship between prior vaccination, immunocompromised status, and risk of VZV reactivation post-COVID vaccination. Furthermore, an epiphenomenon cannot be ruled out since the registry is not designed to establish the incidence of zoster in the vaccinated group or compare it to the incidence in a non-vaccinated group.

VZV reactivation after COVID vaccination has been reported in case reports and small case series,[4–7] and it has also been reported after other vaccines, including yellow fever, hepatitis A,

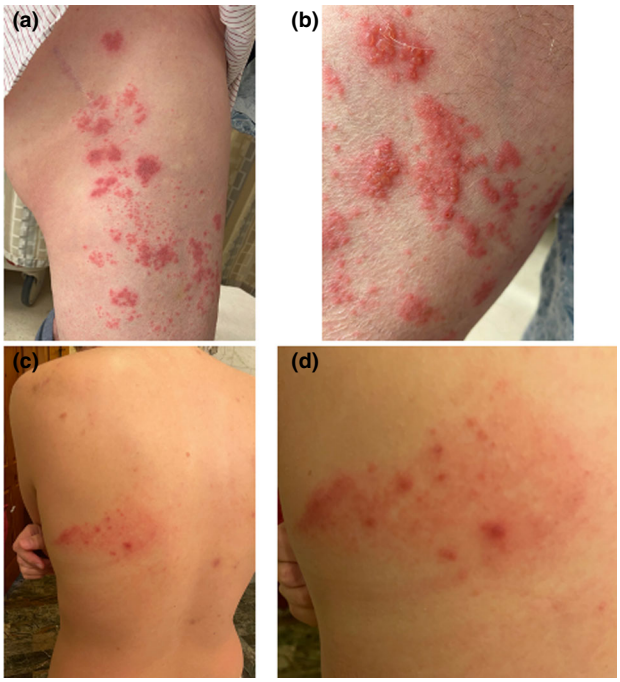

Figure 1 Representative images of Varicella-Zoster Virus reactivation following COVID-19 vaccination. (a) Zoster flare on leg of a patient 14 days after the second dose of Pfizer COVID-19 vaccination (b) same patient, close-up view of vesicles. (c) Zoster flare on the back of a patient 18 days after the first dose of Pfizer COVID-19 vaccination (d) same patient, close-up view of dermatome.

rabies and influenza.[8] While other cutaneous vaccine reactions reported to the registry occurred primarily after Moderna, such as delayed large local reactions,[9] VZV reactivation events occurred after both Moderna and Pfizer in similar proportions in this study, suggesting that reactivation may be the result of an immune reaction process to mRNA vaccines in general. Although the precise mechanism is not known, herpesvirus reactivation may occur due to innate- or cell-mediated immune defense failures initiated by the host response to vaccination. VZV reactivation has also been reported following SARS-CoV-2 infection itself, and a similar immunosuppressive mechanism has been suggested.[10]

Overall, COVID-19 vaccination is still recommended, as the benefits of COVID-19 vaccination vastly outweigh the potential risk of herpesvirus reactivation. Further research is needed to elucidate the risk factors for and mechanisms underlying this process. We advise healthcare workers to be aware of this potential consequence and to begin appropriate treatment when reactivation is suspected.

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Conflicts of interest

Drs. Freeman, Hruza, Rosenbach, Lipoff and Fox are part of the American Academy of Dermatology (AAD) COVID-19 Ad Hoc Task Force. Dr. French is the President, and Dr. Lim is board member of the ILDS. Dr. Thiers is the outgoing President of the AAD. Dr. Freeman is an author of COVID-19 dermatology for UpToDate. Dr. Freeman receives grant support from the ILDS for the COVID-19 Dermatology Registry. Dr. Freeman is a co-author for UpToDate on COVID-19 Dermatology.

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